REMARKS

Claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42, and 78 were pending. Claims 9, 10, 15, 17, 23, 24, 28, 29, 30, 31, 32, and 35 have been canceled hereinabove. Accordingly, only claims 1, 3, 5-8, 18-19, 37-42, and 78 are pending and being examined.

APPLICANTS' CLAIMED INVENTION

The claimed invention provides the following.

> A method for **inhibiting T cell proliferation** comprising contacting CD28 positive T cells with B7 antigen or an anti-CD28 monoclonal antibody so as to bind the CD28 receptor on the CD28 positive T cells with **B7 antigen or an anti-CD28 monoclonal antibody** and thereby inhibiting T cell proliferation.
>
> A method of **inhibiting CD28 positive T cell proliferation** comprising reacting B7 positive cells with a monoclonal antibody designated BB-1 or a $F(ab')_2$ fragment thereof or the CD28Ig fusion protein and thereby blocking B7-T cell interaction and inhibiting CD28 positive T cell proliferation.
>
> A method for preventing the binding of the CD28 receptor to the B7 antigen comprising **contacting CD28 positive T cells with a fragment or derivative of the extracellular domain of the B7 antigen so as to bind the CD28 receptor on the CD28 positive T cells with the fragment or derivative of the extracellular domain of the B7 antigen** thereby preventing binding of the receptor to the B7 antigen.

The claimed methods provide the use of B7Ig and CD28Ig fusion proteins, or fragments thereof, and monoclonal antibodies directed against the CD28 and B7 antigens, each having the characteristics described in the claim.

PARAGRAPHS 21 AND 23 OF OFFICE ACTION

The Examiner objected to the specification under 35 U.S.C. §112, first paragraph, as allegedly failing to provide an adequate written description of the invention and for failing to adequately teach how to make and/or use the invention, i.e., for failing to provide an enabling disclosure. Specifically, the claims are rejected as lacking patentable utility. Further, the Examiner rejected claims 1, 3, 5-10, 15, 17-19, 23-24, 28-32, 35, 37-42 and 78 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

In response, applicants canceled claims 9-10, 15, 17, 23-24, 28-32, 35, and 37-40 without prejudice. With regard to remaining claims 1, 3, 5-8, 18-19, 41-42, and 78, applicants respond as follows.

THE LEGAL STANDARD FOR 35 U.S.C. §112, FIRST PARAGRAPH

The PTO must have adequate support for its challenge to the credibility of applicants' statements as to utility under 35 U.S.C. §112, first paragraph[1]. The guidelines on utility and enablement provides that the Patent Office "must treat as true a statement of fact made by applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement"[2].

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[1] In re Brana et al., 34 USPQ2d 1438 (CAFC 1995).

[2] U.S. Patent and Trademark Office Utility Examination Guidelines, 60 F.R. 36263 (July 14, 1995), 50 PTCJ 295.

In Brana, the court strongly disapproved of the citation of general references to challenge the credibility of applicants' statements when the references do not provide sufficient information to lead one of ordinary skill in the art to doubt the efficacy of the claimed invention but only provides general conclusory statements expressing doubt as to the efficacy of a treatment method or in vitro test or its correlation with the treatment of human disease.

Specifically, the court indicated that:

> "In the context of this case, the Martin and Padzur references, on which the Commissioner relies, do not convince us otherwise. Padzur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of in vivo murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e., the lack of predictive reliability) is not tenable in light of present information" (In re Brana at page 1442).

Clearly, general references do not establish a sufficient showing that one of ordinary skill in the art would reasonably doubt the asserted utility and thus shift the burden to applicants to provide rebuttal evidence.

Situations where an invention is found to be "inoperative" and therefore lacking in utility are rare, and rejections maintained solely on this ground by a Federal court even rarer. In many of these cases, the utility asserted by the applicant was thought to be "incredible in the light of the knowledge of the art, or

factually misleading" when initially considered by the Office.[3] Other cases suggest that on initial evaluation, the Office considered the asserted utility to be inconsistent with known scientific principles or "speculative at best" as to whether attributes of the invention necessary to impart the asserted utility were actually present in the invention.[4] However cast, the underlying finding by the court in these cases was that, based on the factual record of the case, it was clear that the invention could and did not work as the inventor claimed it did. Indeed, the use of many labels to describe a single problem (e.g., an assertion regarding utility that is false) has led to some of the confusion that exists today with regard to a rejection based on the "utility" requirement. Examples of such cases include: an invention asserted to change the taste of food using a magnetic field,[5] a perpetual motion machine,[6] a flying machine operating on "flapping or flutter function,"[7] a method for increasing the energy output of fossil fuels upon combustion through exposure to a magnetic field,[8] uncharacterized compositions for curing a wide array of cancers,[9] a method of

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[3]In re Citron, 325 F.2d 248, 253, 139 USPQ 516, 520 (CCPA 1963).

[4]E.g., In re Sichert, 566 F.2d 1154, 196 USPQ 209 (CCPA 1977).

[5]Fregeau v. Mossinghoff, 776 F. 2d 1034, 227 USPQ 848 (Fed. Cir. 1985).

[6]Newman v. Quigg, 877 F.2d 1575, 11 USPQ2d 1340 (Fed. Cir. 1989).

[7]In re Houghton, 433 F.2d 820, 167 USPQ 687 (CCPA 1970).

[8]In re Ruskin, 354 F.2d 395, 148 USPQ 221 (CCPA 1966).

[9]In re Citron, 325 F.2d 248, 139 USPQ 516 (CCPA 1963).

controlling the aging process,[10] and a method of restoring hair growth.[11] Thus, in view of the rare nature of such cases, Office personnel should not label an asserted utility "incredible," "speculative" or otherwise unless it is clear that a rejection based on "lack of utility" is proper.

Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is *credible* (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility.

One situation where an assertion of utility would not be considered credible is where a person of ordinary skill would consider the assertion to be "incredible in view of contemporary knowledge" and where nothing offered by the applicant would counter what contemporary knowledge might otherwise suggest. Office personnel should be careful, however, not to label certain types of inventions as "incredible" or "speculative" as such labels do not provide the correct focus for the evaluation of an

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[10]In re Eltgroth, 419 F.2d 918, 164 USPQ 221 (CCPA 1970).

[11]In re Ferens, 417 F.2d 1072, 163 USPQ 609 (CCPA 1969).

assertion of utility. *"Incredible utility" is a conclusion, not a starting point of analysis under § 101.* A conclusion that an asserted utility is "incredible" can be reached only after the Office has evaluated both the assertion of the application regarding utility *and* any evidentiary basis of that assertion. The Office should be particularly careful not to start with a presumption that an asserted utility is *per se* "incredible" and then proceed to base a rejection under § 101 on that presumption.

APPLICANTS HAVE MET THE LEGAL STANDARD

SUBPARAGRAPH A

Applicants respectfully contend that the cited references do not provide countervailing evidence that shows one skilled in the art would have a legitimate basis to doubt the credibility of applicants' asserted utility, namely, that the use of Ig fusion proteins and monoclonal antibodies recited in the claimed methods would inhibit T cell proliferation.

Clearly, applicants have established that Ig fusion proteins have in fact inhibited T cell proliferation (see Lenschow et al. already of record). Even the cited references support the operability of monoclonal antibodies as therapeutic agents as discussed hereinafter. For these reasons applicants contend that the cited references do not provide conterveiling evidence in accordance with the Examiner's position.

A. THERE IS NOTHING INHERENTLY UNBELIEVABLE OR IMPLAUSIBLE ABOUT THE USE OF MONOCLONAL ANTIBODIES IN THERAPY

Contrary to the Examiner's position, there is nothing in the

nature of applicants' invention alone which would cause one of skill in the art to reasonably doubt the asserted usefulness. The use of antibodies as immunosuppressive agents is well established (R. Handschumacher "Chapter 53: Drugs Used for Immunosuppression" at pages 1264-1276, pages 1272-1273 annexed herewith as Exhibit 1). Therefore, the claimed methods do not contravene established scientific principles[12].

THE USE OF PROTEINS IN CLINICAL THERAPY IS WIDESPREAD

Modern science has previously identified numerous successful protein agents. For example, the clinical use of interferon as an antineoplastic agent is well established[13]. Additionally, the clinical use of recombinant erythropoietin (EPO) to treat renal failure is well established (R. Williams "Chapter 8: Hematopoietic System, Recombinant Products, and Clinical Applications" in Molecular Biology in Clinical Medicine (1991) pages 269-327 annexed herewith as Exhibit 2). Further, the clinical use of recombinant factor VIII to induce thrombin formation and normal clotting is well established (Exhibit 2 at page 287); as is the clinical use of t-PA to stop clotting (Exhibit 2 at page 317).

There is no reason to doubt that Ig fusion proteins are will bind its receptor in vivo thereby inhibiting T cell proliferation in

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[12] Alleged operability seems clearly to conflict with recognized scientific principles as, e.g., when applicant purports to have discovered a machine producing perpetual motion, the presumption of inoperability is so strong that very clear evidence is required to overcome it (In re Marzocchi & Horton, 169 USPQ2d 367).

[13] Ex parte Rubin, 5 USPQ2d 1461 (BPAI 1987).

view of the success in vivo of CTLA4Ig as an immunosuppressant. CTLA4 is homologous to CD28.

ANTIBODIES WHICH INDUCE A HAMA RESPONSE ARE THERAPEUTICALLY USEFUL

Specifically, the use of antibodies in clinical therapy is widespread. In fact, several preparations of antibodies have been approved as immunosuppressive agents (Exhibit 1 at pages 1272-1273). Some of these interact with lymphoid cells, leading either to blockade of their function (OKT3) or to their destruction (antithymocyte globulin). Most currently available preparations are from nonhuman sources and, hence, incur the potential for the development of anti-idiotypic antibodies even in their immunosuppressed host upon repeated administration. Nevertheless, their ability to lower the number and suppress the function of selected types of normal lymphoid cells has provided an important means to treat acute episodes of rejection in recipients of transplanted organs, as well as to prevent (and treat) graft-versus-host reactions in recipients of bone marrow transplants.

SOLUTIONS TO REMEDYING THE PROBLEMS DESCRIBED IN THE PRIOR ART DO NOT INVOLVE UNDUE EXPERIMENTATION SINCE THE READY AVOIDANCE OF THE PROBLEMS WOULD HAVE BEEN WITHIN THE LEVEL OF ONE HAVING ORDINARY SKILL IN THE ART[14].

At the outset applicants respectfully point out that some of the claimed methods are directed to the use of Ig fusion proteins.

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[14] There is no undue experimentation when the ready avoidance of a result would be within the level of one skilled in the art (In re Marzocchi & Horton, supra).

Applicants respectfully contend that the cited references are inapplicable to challenge the credibility of the use of Ig fusion proteins since they are not antibodies. Further, the Ig portion of the fusion protein is human.

With regard to methods using monoclonal antibodies, applicants respectfully contend that the cited references are deficient to challenge the credibility of the utility of applicants' claimed methods for the following reasons.

The cited references do not involve analogous art. The use of the monoclonal antibodies reviewed in the references were directed to solid tumors. Applicants respectfully traverse the Examiner's position that the general teachings presented in the Dillman, Hird, and Osband references, regarding the application of antibodies, is applicable to any in vivo method, despite the fact that these references are directed to cancer treatment.

The Examiner's position is misplaced. As pointed out hereinabove, the court in Brana strongly disapproved of the citation of general references to challenge the credibility of applicants' statements when the references do not provide sufficient information to lead one of ordinary skill in the art to doubt the efficacy of the claimed invention but only provides general conclusory statements expressing doubt as to the efficacy of a treatment method or in vitro test or its correlation with the treatment of human disease. Clearly, general references, without more, do not establish a sufficient showing that one of ordinary skill in the art would reasonably doubt the asserted utility and thus shift the burden to applicants to provide rebuttal evidence.

At most the cited references report limitations associated with the use of MAbs in treating solid tumors. It is important to point out that not one claim of this application requires the killing of any tumor cells or the elimination or shrinkage of any masses of tumor tissue. All that these claims require is that T cell proliferation be inhibited.

Waldman, Harris et al., Osband et al., Dillman do not challenge the credibility of applicants' statements of utility under 35 U.S.C. §112, first paragraph. Instead, these references discuss the drawbacks associated with the use of unmodified murine monoclonal antibodies in clinical therapy **and** solutions to the problem, e.g., developing human or humanized antibodies that are less immunogenic than their murine counterparts.

At most these references question whether unmodified murine monoclonal antibodies should be used in therapy. The references do not question the usefulness of modified antibodies in therapy and whether such modifications would involve undue experimentation.

For the reasons discussed above, applicants take the position that the Patent Office has not established, on the basis of technical information from the cited references, that the operability of the invention as described in the application would have been regarded as "incredible" by the person of skill in the pertinent art on the effective filing date of the application.[15]

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[15]In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971); In re Gazave, 379 F.2d 973, 154 USPQ 92 (CCPA 1967); In re Isaacs, 347 F.2d 887, 146 USPQ 193 (CCPA 1965); Ex parte Rubin, 5 USPQ2d 1461 (BPAI 1987). See also In re Bundy, 209 USPQ 48 (CCPA

B. THE EFFECT OF CONFLICTING REFERENCES

Contrary to the Examiner's position, applicants do not concede that the Harris, Waldman, Dillman, Osband, and Hird references teach that there is a high level of unpredictability in the field of using monoclonal antibodies in clinical therapy in view of the Thorpe, Hird, and/or Dillard references.

The Thorpe, Hird, and/or Dillard references contradict the Examiner's interpretation of the teachings of the Waldman, Osband, and Harris references. Moreover, even if they do not contradict the Examiner's interpretation, the fact that all of the references except Waldman are directed to reporting the use of monoclonal antibodies as solid tumor cancer therapies should not discredit applicants' assertion of utility (how to use the monoclonal antibodies and Ig fusion proteins as immunosuppressants of the claimed methods), especially in view of the fact that Waldman reports that monoclonal antibodies are effective immunosuppressants **as claimed**.

There is nothing in the nature of applicants' invention alone, i.e., methods for immunosuppression, that would cause one of skill in the art to reasonably doubt the asserted usefulness. At most the cited references cast a shadow over the use of monoclonal antibodies in solid tumor cancer therapy but not immune therapy.

Once again applicants point out that only Waldman discloses the use of monoclonal antibodies on modulation of the immune response

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1981) and In re Chilowsky, 229 F.2d 457, 108 USPQ 321 (CCPA 1956).

(Waldman at page 1654, abstract; page 1657, right column, first and second full paragraphs). In this regard Waldman teaches that such monoclonal antibodies are **effective** immunosuppressive agents (Waldman at page 1658, left column, third full paragraph).

Dillman, Hird, and Osband disclose the use of monoclonal antibodies only in the context of cancer (Harris at page 43; Dillman at page 592, left column, first sentence; Dillman at page 592, left column, fifth full paragraph; Dillman at page 591, sentence bridging left and right columns; Dillman at page 594, right column, second full sentence; Dillman at page 594, right column, third full sentence, first paragraph; Dillman at page 594, right column, first paragraph, fourth full sentence; Dillman at page 594, right column, first full paragraph; Dillman at page 597, right column, first full paragraph; Hird at page 185, second full paragraph, fourth sentence; Hird at page 189; Osband at page 193, left column, abstract, second sentence; Osband at page 194, left column, second and third full paragraph).

Further, the fact that applicants provide the Thorpe, Hird, and/or Dillard references to rebut the Examiner's position should be sufficient to overcome the rejection. To hold otherwise would be illogical.

The holding of Brana makes it clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. In this regard, the Thorpe, Hird, and/or Dillard references, alone or in combination, contradict the Examiner's interpretation of the teachings of Waldman, Osband, and Harris references. Therefore, the Thorpe, Hird, and/or Dillard references provide evidence sufficient to affirm the utility of applicants' claimed methods

under 35 U.S.C. §112, first paragraph. Applicants have met their burden and the objection and rejection should be withdrawn.

Moreover, even were applicants to concede that the Examiner's position was correct and the use of monoclonal antibodies involved an incredible undertaking. Brana supports the contention that in vitro data is effective rebuttal evidence sufficient to convince one of skill in the art of the asserted utility. Accordingly, applicants' in vitro data set forth in Example 3 of the specification at page 64, lines 5-35 and pages 65-72, rebuts the Examiner's position.

C. IN VITRO DATA IS SUFFICIENT FOR ENABLEMENT

As shown in Figure 16, B7Ig blocked CD28-mediated adhesion somewhat less effectively than mAb 9.3 (half-maximal inhibition at 200 nM as compared with 10 nM for mAb 9.3) (specification at page 64, lines 21-23). The relative effectiveness of these molecules at inhibiting CD28-mediated adhesion was similar to their relative binding affinities in competition binding experiments (Figure 12) (specification at page 64, lines 23-25). CD28Ig failed to inhibit CD28-mediated adhesion at concentrations of up to 950 nM, suggesting that much higher levels of CD28Ig were required to compete with the high local concentrations of CD28 present on transfected cells (specification at page 64, lines 27-30).

Binding of B7 to CD28 on T cells was costimulatory for T cell proliferation (Tables 2-4) suggesting that some of the biological effects of anti-CD28 mAbs result from their ability to mimic T cell activation resulting from natural interaction between CD28 and its counter-receptor, B7 (specification at page 71, lines 5-

9).

CD28/B7 interactions may also be important for B cell activation and/or differentiation. As described above in Example 2, mAbs 9.3 and BB-1 block T_h cell-induced Ig production by B cells (specification at page 71, lines 28-29). This blocking effect may be due in part to inhibition by these mAbs of production of T_h-derived B cell-directed cytokines, but may also involve inhibition of B cell activation by interfering with direct signal transduction via B7 (specification at page 71, lines 29-31). These results suggest that cognate activation of B lymphocytes, as well as T_h lymphocytes, is dependent upon interaction between CD28 and B7 (specification at page 71, lines 31-35).

In accordance with Brana, such in vitro evidence alone should be sufficient to satisfy applicants' burden[16].

D. CTLA4Ig IS A STRUCTURALLY SIMILAR MOLECULE TO CD28Ig

Further, post filing data provides additional support for the conclusion that one skilled in the art would be convinced of applicants' asserted utility. As previously discussed, the Lenschow reference (D. Lenschow et al. ((1992) Science 257:789-792 entitled "Long Term Survival of Xenogeneic Pancreatic Islet Grafts Induced by CTLA4Ig" already of record) disclosed structurally similar compounds, namely, CTLA4Ig which blocked the CD28 receptor from binding the B7 antigen in mouse thereby resulting in manipulating the mouse immune system into accepting transplanted tissue instead of attacking it and thereby preventing the rejection of transplanted tissue.

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[16] In re Brana at page 1442.

Clearly, it is well established that evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility[17]. The court in Brana clearly supports the holding that testing for full safety and effectiveness of the claimed invention is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of PTO proceedings.

SUBPARAGRAPH B

The Examiner objects that the disclosure provides only a description of B7 antigen on CHO cells. Other immobilized B7 sources have not been enabled by the specification for applicants' claimed invention.

In response, applicants have canceled claims 9 and 10. The objection should be rendered moot.

SUBPARAGRAPH C

The Examiner objects that the disclosure does not provide an enabling description of a method having the steps of reacting B-cells with T-cells.

In response, applicants have canceled claim 17. The objection should be rendered moot.

SUBPARAGRAPH D

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[17] In re Brana at page 1442; Rey-Bellet v. Engelhardt, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974); Kawai, 480 F.2d880, 178 USPQ 158.

The Examiner objected to the disclosure because it allegedly does not provide an enabling description of fusion proteins of at least a portion of the extracellular domain of the CD28 receptor. The disclosure is specifically directed to a fusion containing amino acid residues, of the CD28 receptor, from about position 1 to 134 and a second amino acid sequence corresponding the hinge, CH2 and CH3 regions of human IgG1 constant domains.

In response, applicants point out that only claims 28, 29, 30, and 32 recite use of fusion proteins of at least a portion of the extracellular domain of the CD28 receptor. These claims have been canceled without prejudice. Accordingly, the rejection is rendered moot.

SUBPARAGRAPH E

Applicants have canceled claim 15. Therefore, the anti-CD2 issue raised by the Examiner is rendered moot.

Further, contrary to the Examiner's position, applicants' specification does support a method of inhibiting T cell proliferation with any B7 antigen derivative. It is a well established tenet of patent law that "a patentee need not describe all possible embodiments of his invention...."[18]

Applicants are justly entitled to more than the use of B7Ig. Clearly, the invention is directed to the discovery that B7 will recognize CD28 and that this recognition produces the claimed result. B7Ig is but one embodiment of soluble B7 molecules (which bind to CD28). Once those skilled in the art knew

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[18] Kesling v. General Motors Corporation, 66 F. Supp. 1.

applicants' discovery, it is well within their skill to make other soluble B7 molecules which bind to CD28 to effect the same result as that which applicants' achieved using B7Ig.

Applicants respectfully contend that applicants need not teach what is well known in the art[19]. Methods of making recombinant proteins, e.g., soluble proteins, were well known to those skilled in the art well before applicants' invention.

THE INVENTION LIES IN THE DISCOVERY THAT THE COUNTER RECEPTOR FOR THE B7 MOLECULE IS CD28

Using the discovery that the counter receptor for the B7 molecule is CD28, it would have been routine to make and use recombinant B7 proteins capable of binding CD28. Identifying recombinant soluble B7 proteins which bind to CD28 merely involves setting up competition assays in which the B7Ig of the present invention used to compete with other embodiments of soluble B7 proteins for CD28. Competition assays are routinely done and their protocols are clearly within the skill of one in the art (E. Harlow and D. Lane, eds., "Antibodies a laboratory manual" 1988, pages 567-577 already of record as Exhibit 2 of applicants' December 13, 1993 response).

Any recombinant B7 proteins having at least a portion of the B7 antigen which recognizes and binds CD28 fall within the scope of this invention.

In fact, the general technique for construction of expression vectors for fusion proteins were well known in the art (Ernst

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[19] Staehelin v. Secher, 24 U.S.P.Q.2d 1513, 1516 (Bd. Pat. App. & Int. 1992).

Winnacker, "From Genes to Clones: Introduction to Gene Technology" Chapter 7, (1987) at pages 279-305 which will be sent to the Patent Office shortly).

The general approach for the construction of expression vectors directing the synthesis of fusion proteins is as follows (Ernst-L. Winnacker, "From Genes to Clones: Introduction to Gene Technology" (1987) Chapter 7 at pages 239-317, 291).

The starting material can be a B7 cDNA clone whose B7 insertion has been removed from a vector (Ernst-L. Winnacker, "From Genes to Clones: Introduction to Gene Technology" (1987) Chapter 7 at page 291). Using methods known in the art a restriction site is positioned close to a start codon. The next step is a digestion step which should cut DNA fragments asymmetrically. The mixture of DNA fragments obtained is then cloned into a vector, e.g., a pUC vector. Of course, a cleavage site must be present within the polylinker of the chosen vector. Since a wide spectrum of vectors is available, it should not be difficult to find a suitable vector containing the desired cleavage site. Once a suitable clone is identified, the cleavage site can be used for the insertion of the gene of interest, which can be obtained from the original cDNA clone.

Applicants respectfully contend that the DNA and amino acid sequence for B7 was published before the filing date of the subject application. Therefore, it would have been routine to generate B7 fusion proteins for the claimed methods (Sambrook et al., eds., Molecular Cloning, A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory Press (1989)).

SUBPARAGRAPH F

The Examiner has taken the position that applicants' specification does not support the scope of claims directed to a method for preventing the binding to the CD28 receptor to the B7 antigen.

Applicants respectfully disagree with the Examiner's position. However, in order to further the prosecution of the subject application, applicants have canceled claim 35 and amended claims 37-40 to depend on claim 1. Accordingly, the objection and rejection have been rendered moot.

SUBPARAGRAPH G

The Examiner alleged that it is unclear from the specification how the methods of claims 9, 10, 15, 17, 35 and 38 will result in inhibiting T cell proliferation.

Applicants point out that claims 9, 10, 15, 17, and 35 have been canceled without prejudice. Moreover, claim 38 has been amended to depend on claim 1. Accordingly, the rejection is rendered moot.

SUBPARAGRAPH H

Applicants respectfully point out that the Examiner's observation that "Since applicants' invention is not limited to <u>in vitro</u> use it would be expected that the anti-CD28 mAb would be cross-linked <u>in vitro</u> thereby activating the T-cell" is irrelevant.

Damle et al. teach the use of the anti-CD28 mAb 9.3 as a means of inhibiting T-cell proliferation. In addition, Damle et al. show that when a novel, biologically active reagent (mAb 187.1, a

commercially available monoclonal generated in rats and specific for murine kappa light chain) is added to the mixed lymphocyte reaction (MLR), this reagent will influence the biological processes in vitro. These in vitro experiments which involve the addition of a highly specific antibody selected for its reactivity to mAb 9.3 do not provide evidence that 9.3 will be cross-linked in other biological systems.

Furthermore, while the unique idiotope of every antibody molecule has the potential of being immunogenic within all novel milieus, the theoretical possibility of an antibody being recognized as foreign and subsequently cross-linked should not be a bar to enablement. 35 U.S.C. § 112, first paragraph requires only that applicants teach how to make and use the claimed invention. Applicants teach how to make and use the claimed invention and their data supports this claim (specification at page 31, lines 5-13; page 34, lines 4-13; page 45, lines 23-27; page 47, lines 1-22; page 71, lines 14-26).

SUBPARAGRAPH I

Contrary to the Examiner's position, the fact that the claimed method does not contemplate CTLA4 does not render suspect the predictability or operability of the claimed method. It is well established caselaw that applicants need not understand the theory or scientific principle underlying his invention; all that he need do is to enable a person skilled in the art to duplicate his efforts[20].

In this regard, applicants' in vitro data shows that T cell

[20] In re Isaacs and Lindenmann, 146 USPQ 193 (CCPA 1965).

proliferation has been effected using the CD28/B7 pathway. For example, Figure 6 shows that the presence of anti-CD28 mAb (9.3 IgG2a) but not that of isotype-matched anti-CD7 mAb (4H9, IgG2a) consistently inhibited the MLR proliferative response of $CD4^+$ T cells to allogeneic B cells (specification at page 47, lines 1-5).

Similarly, the addition of anti-B7 mAb (BB1; IgM) but not that of isotype-matched anti-CD57 HNK1; IgM) to the allogeneic MLR resulted in the inhibition of T cell proliferation (specification at page 47, lines 5-9).

Similar to the allogeneic MLR, proliferative response of $CD4^+$ T cells to soluble Ag PPD presented by autologous non-T cells was also inhibited by anti-CD28 and anti-B7 mAb (specification at page 12, lines 9-15).

The results in the specification demonstrate the relationship of CD28 receptor and its ligand, the B7 antigen, as a co-stimulatory transmembrane receptor-ligand pair influencing T_h:B interactions (specification at page 50, lines 30-35; page 51, lines 1-4). Involvement of both CD28 and B7 during T_h:B collaboration was demonstrated by inhibition by anti-CD28 and anti-B7 of not only T_h cell activation but also T_h-induced differentiation of B cells into IgSC (specification at page 50, lines 32-35). It appears as if the observed inhibitory effects of anti-CD28 and anti-B7 mAbs are due to the inhibition of CD28:B7 interaction underlying these responses (specification at page 51, lines 1-4).

Anti-CD28 mAbs are inhibitory for antigen-specific T cell responses (specification at page 71). This may indicate that antigen-specific T cell responses are dependent upon

costimulation via CD28/B7 interactions, and that inhibition therefore results from blocking of CD28 stimulation.

Applicants respectfully contend that applicants have enabled a person skilled in the art to duplicate his efforts in accordance with 35 U.S.C. §112. Accordingly, the objection and rejection should be withdrawn.

PARAGRAPH 26

The Examiner rejected claims 1, 3, 5-8, 18, 23, 24, 41 and 42 under 35 U.S.C. § 103 as allegedly unpatentable over Linsley et al. [PNAS 87:5031-5035 (1990)] and Freeman et al. [J. Immunology 143:2714-1722 (1989)] in view of Capon et al. [WO 89/02922] for reasons of record.

Applicants respectfully disagree with the Examiner's basis for rejecting these claims. However, in order to further the prosecution of the subject application, applicants will provide a Declaration by Peter S. Linsley, Jeffrey A. Ledbetter, Nitin K. Damle, and William Brady under 37 C.F.R. §1.132 stating that they are the true inventors of the claimed methods and that some of their co-authors in Linsley et al., Proc. Natl. Acad. Sci. 87:5031-5035 (1990) were correctly omitted as inventors of the claimed methods.

In view of the attached declaration, the Linsley reference must be withdrawn from the combination. Further, without the Linsley reference, the combination fails and the rejection should be withdrawn.

PARAGRAPH 27

The Examiner rejected claims 19 and 78 under 35 U.S.C. § 103 as allegedly unpatentable over Linsley et al. [PNAS 87:5031-5035 (1990)] and Aruffo et al. [PNAS 84:8573-8577 (1987)] in view of Capon et al. [WO 89/02922] for reasons of record.

In view of the Declaration, the Linsley reference should be withdrawn from the combination. Therefore, the rejection fails and should be withdrawn.

PARAGRAPH 28

The Examiner rejected claims 9, 10, 15 and 17 under 35 U.S.C. §112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, applicants have canceled claims 9, 10, 15, and 17 without prejudice.

PARAGRAPH 29

The Examiner rejected claims 28-34 under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, applicants point out that of claims 28-34 only claims 28-32 were pending in the subject application. In this regard, applicants have canceled claims 28-32 without prejudice.

PARAGRAPH 31

The Examiner rejected claims **35** and 37-40 under 35 U.S.C. § 102(b) as allegedly anticipated by Ledbetter et al. [J.I. 135(4):2331-2335 (1985)] for reasons of record.

Applicants respectfully disagree with the Examiner's position. However, in order to further the prosecution of the subject application, applicants have canceled claim 35 and amended claims 37-40 to depend on claim 1. These changes should obviate the rejection. However, applicants wish to state the following for the record.

Ledbetter et al. teach that anti-CD28 augments T cell proliferation thereby sustaining T cell growth over an extended period of time (Ledbetter at page 2334, left column, third paragraph; page 2331, right column, first full paragraph, lines 5-8 and page 2332, right column, last paragraph). Nowhere does Ledbetter teach that anti-CD28 MAbs inhibit T cell proliferation.

The Examiner states that "a Fab to CD28 will inhibit T cell proliferation due to blocking any ligand, including B7, from binding the CD28 receptor while the Fab is bound. It is not necessary for recognition of the B7 ligand to be known, the Fab will block any CD28 ligand, inherently including B7."

It is incorrect to state that the "Fab to CD28 will inhibit T cell proliferation due to blocking any ligand, including B7, from

binding the CD28 receptor while the Fab is bound." The authors did not know that at the time. The Examiner can only make that statement based on knowledge gleaned from the specification.

The fact that it would have been inherent for anti-CD28 MAbs to inhibit T cell proliferation is irrelevant in the context of the claims. Although it is well established caselaw that inherency can be used to establish anticipation of claims reciting process or methods, where a method or process step or result is inherent in the prior art, it is also well established that there are exceptions to the general rule that a prior use, existence or practice will anticipate. These exceptions generally involve things which were not fully appreciated before their discovery by applicants[21].

In Marshall, the court held that "accidental or unwitting duplication of invention cannot constitute anticipation". In the Marshall case, the methods involved use of compounds for esophagitis, gastritis, peptic ulcer and irritable colon syndrome; whereas, the claimed method used the same compound for weight loss. The court held that if "anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot consitute an anticipation."

Clearly, in Marshall regardless of the fact that the use of the compounds in weight loss would have been inherent, the inherency argument was irrelevant. The issue was whether the prior art understood the invention, i.e., use of the compound for weight loss. The court held it did not and overruled the rejection.

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[21] In re Marshall 198 U.S.P.Q.344 (CCPA 1978).

Comparatively, in our case, applicants' invention is directed to inhibiting T cell proliferation using among other thing anti-CD28 MAbs. In contrast, the prior art used anti-CD28 MAbs to stimulate T cell proliferation. This is totally contrary to the claimed invention.

Like Marshall, applicants contend that the fact that it would have been inherent for anti-CD28 MAbs to inhibit proliferation is irrelevant. For these reasons applicants respectfully contend that the rejection is improper and should be withdrawn as to claims 37-40.

PARAGRAPH 32

The Examiner rejected claims 35 and 37-40 under 35 U.S.C. § 102(b) as allegedly anticipated by Damle et al. [J.I. 140(6):1753-1761 (1988)] for reasons of record.

Applicants respectfully disagree. However, in order to further the prosecution of the subject application, applicants have canceled claim 35 and amended claims 37-40 to depend on claim 1. These changes should obviate the rejection. However, applicants wish to state the following for the record.

Applicants respectfully point out that this rejection was previously made and withdrawn in 1992. The rejection was first issued in an Office Action dated March 25, 1992. On August 24, 1992, applicants filed a response including amendments to claim 35 and providing arguments traversing the rejection (see pages 3 and 15-17 of applicants' August 24, 1992 response). In turn, the Examiner withdrew the rejection in an Office Action dated December 4, 1992 (see page 10, paragraph 56 of December 4, 1992

Office Action).

Applicants stated then and the Examiner agreed (as evidenced by the withdrawal of the rejection) that Damle teaches that the anti-CD28 monoclonal antibody in its intact form or its F(ab')2 fragments had a strong growth-promoting effect on both anti-CD3-induced and IL-2 induced proliferation (Damle at page 1758, second column, second full paragraph, lines 14-17).

Damle teaches that the inhibitory effect of anti-CD28 mAb on the development of CTL in the MLR could be due to the inhibition of clonal expansion (proliferation) of CD8+CD28+ precursors of CTL in addition to that of CD4+CD28+helper/inducer cells that provide the necessary growth- and differentiation- inducing factors such as IL-2 (Damle et al. at page 1755, second column, second full paragraph, last sentence). Damle did not teach or suggest the interaction of the B7 antigen with the CD28 molecule. Therefore, the Damle reference does not anticipate the claimed invention.

Applicants respectfully contend that because **the** critical advantage of the claimed method is the realization that the B7 antigen specifically interacts with the CD28 receptor, the Damle does not and could not have suggested the claimed method.

In view of Applicants' preceding comments Applicants request that the Examiner reconsider and withdraw the rejection to the claims.

No fee, other than the extension fee, is deemed necessary in connection with the filing of this response. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 13-2724.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Sarah B. Adriano 8-28-95

Signature Date